Observations on the Effect of Cortisone in a Case of Phenylpyruvic Oligophrenia

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IN 1953 BEFORE DIETS for the control of phenylketonuria had been introduced, an intensive trial of cortisone therapy was given in a case of phenylpyruvic oligophrenia to determine whether or not this drug would eliminate the excretion of phenylpyruvic acid in the urine. Although the elimination of phenylketonuria was not accomplished, the effect of the drug on other manifestations of the disease may be of interest now since the use of a phenylalanine-free diet early has given evidence that children with this metabolic disturbance may have a chance to develop without extreme retardation.

REPORT OF A CASE

The patient, a girl born January 9, 1952, was the second child of young, healthy parents. There had been no abnormality in pregnancy, labor or birth. A sister two years older was living and well. Cousins of the patient had been put in institutions because of mental retardation (type unknown).

At two weeks of age the patient had a facial rash which later extended over the trunk and extremities. At three months of age the mother was concerned about the child's vision because of failure to watch the movement of objects. At five months it was obvious that the child was retarded in motor development and awareness. At this time also she had occasional brief jerking movements of the extremities. The rash had improved but remained over the cheeks, and there was evidence of generalized pruritus although the skin was not broken or irritated except on the face.

The child was first seen by the author and admitted to the hospital at the age of 18 months. She was blond and blue eyed and had a fair, rather doughy skin with eczematous patches over the cheeks. The head, which looked slightly microcephalic, was 50 cm. in circumference. The circumference of the chest was 44 cm. The child was 85 cm. long and weighed 27 pounds. The anterior fontanel, which was still patent, was 1.5 by 1.5 cm.

The pupils reacted to light and no abnormalities were observed on fundoscopic examination. A nasal discharge was present. The patient had 16 teeth. The heart and lungs were normal to auscultation and percussion. Unable to sit up, the patient rested in a frog-like position with general atonia of the muscles, but at times she became irritable and restless and thrashed about with purposeless movements. Apparently she did not recognize her mother either by sight or voice. The patient had random convulsive twitchings, with more severe seizures at night when she was dropping off to sleep. Hence getting to sleep was difficult, but once asleep she was not disturbed further through the night.

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Results of urinalysis were within normal limits except for a positive reaction to a phenylpyruvic test. The hemoglobin content of the blood was 11.0 gm. per 100 cc. Erythrocytes numbered 4,030,000 per cu. mm. and leukocytes 12,150 with a differential of 38 per cent polymorphonuclear cells, 53 per cent lymphocytes, 3 per cent eosinophiles and 4 per cent monocytes. The sedimentation rate was 8 mm. in one hour. The number of cells in the spinal fluid and the glucose and protein content were within normal limits. Kolmer and Kahn tests were negative for syphilis. Cephalin flocculation was normal. Cholesterol content was 202 mg. per 100 cc. of serum (normal 120-260 mg.).

In a skeletal survey, bone development was observed to be six or eight months ahead of normal.

An electroencephalogram was reported as diffusely abnormal in mild to moderate degree, compatible with some generalized disturbance or delayed maturation of the brain. A pneumoencephalogram was reported as showing a moderate degree of cerebral atrophy.

A variety of drugs—diphenhydramine hydrochloride, calcium and barbiturates—were given in an attempt to allay itching and control the seizures, but no beneficial effect was noted.

The problem was discussed with an oncologist who was interested in the metabolism of phenylalanine, and he suggested a trial of cortisone alone and then in combination with ascorbic acid. The criteria to be used for evidence of the effectiveness of the drugs were: Disappearance of the excretion of phenylpyruvic acid; alteration in eczema; changes in seizures; mental or physical improvement.

Beginning November 23, 1953, at the age of 23 months and a weight of 27 pounds 10 ounces, the patient was given a five-day test with cortisone alone, as follows: First day, 50 mg.; second day, 100 mg.; third day, 75 mg.; fourth and fifth days, 50 mg. each.

On December 2 the family reported that the child had shown almost immediate improvement. She slept better and seemed more active and alert, and pruritus abated. A test showed no change in the phenylketonuria. Cortisone was continued, 25 mg. twice daily, and the patient was seen again at the end of two weeks. The reports were less enthusiastic than after the first five days. The pruritus remained under control and the patient remained more alert than she had been before cortisone therapy, but she continued to have difficulty in falling asleep at night because of seizures. The phenylpyruvic test reaction remained positive. As seizures continued after three weeks of administration of 50 mg. of cortisone daily, dilantin was given, 50 mg. three times a day, and phenobarbital, 15.0 mg. three times a day, to see whether or not this, with the cortisone, would control them.

At the age of two years and after approximately six weeks of cortisone therapy the patient was reexamined on January 7, 1954. The family of its own accord had discontinued giving dilantin and

phenobarbital because the seizures had not been controlled. The pruritus was under control, there was no eczema, and the patient was more alert, reached for objects and played with some of them, and made some attempts to sit up. The body weight was 28 pounds. Cortisone was continued, 50 mg. daily, and 200 mg. of ascorbic acid was added. On March 13 the status remained the same. It was then decided to try a definitive test with high doses of cortisone and ascorbic acid. As a preparation for this regimen, the ascorbic acid was omitted for three days, and then cortisone alone was given in a dosage of 150 mg. daily for one week. At the end of this period phenylpyruvic acid was still excreted in the urine. With no change in cortisone dosage, ascorbic acid, 500 mg. daily, was added. A urine test after five days of therapy with both drugs still showed phenylketonuria. A few days after the amount of cortisone was increased to 150 mg. daily, the night seizures stopped. There was complete control of eczema and pruritus, and the patient was happy, somewhat playful, able to reach for objects, recognized her parents to a degree and could sit up without support. More or less empirically and because of the reports of seizures due to pyridoxine deficiency, 10 mg. of vitamin B_6 daily, was added to the cortisone and ascorbic acid already being given. At the end of a month, phenylpyruvic acid was still being excreted in the urine. Quantitative tests were not done. Although the general improvement noted earlier continued, it seemed insufficient to warrant continuing the drugs in so high a dosage.

A period of experimentation to find the minimal adequate dose of cortisone was then started. When cortisone was reduced to 25 mg. daily, but the other two drugs maintained at previous levels, eczema returned and the patient became irritable and lost interest in her surroundings. Cortisone was therefore increased to 50 mg. daily and pyridoxine and ascorbic acid were discontinued. A normal diet with adequate content of vitamins was maintained.

Two other unsuccessful attempts to help this child were made. One was the use of reserpine, which did not relieve the restlessness. The other was a phenylalanine-free diet, which she would not eat. The patient was put into an institution in 1955.

DISCUSSION

In retrospect the general improvement of this child on cortisone may be significant. At the time of the experiment, the primary interest was in what effect there might be on the output of phenylpyruvic acid. Throughout the period of experimentation, phenylketonuria continued.

Although it is difficult to separate alterations due to growth and development in a retarded child from effects of therapy, it can be stated that the eczema and general pruritus improved and practically disappeared during therapy. (It must be noted that this is not unique in patients with phenylpyruvic oligophrenia.) The seizures ceased after the dose of cortisone was increased to 150 mg. daily but did not return during a period of observation when it was again reduced to 25 and 50 mg. Hence, an assumption that cortisone therapy per se brought about the improvement must be looked upon skeptically. Finally, the general improvement in awareness, in emotional response and in ability to sit up and reach for objects not only began soon after therapy with the drug was started but definitely lapsed when it was discontinued. The improvement was not sufficient in a profoundly retarded child at the age of two years to warrant hope that development could proceed to any worthwhile degree, and therapy was therefore discontinued except to the extent that it enhanced the comfort of the patient.

SUMMARY

A case of phenylpyruvic oligophrenia is reported in which cortisone, ascorbic acid and pyridoxine alone and in combination were tried.

The urinary excretion of phenylpyruvic acid with cortisone alone or in combination with ascorbic acid and pyridoxine was not changed. The comfort of the child, however, increased during cortisone therapy; eczema and pruritus were controlled and seizures were abated. The patient showed some general growth in mental acuity, emotional status and physical accomplishments. The experiment did not seem promising enough to continue the therapy in this child.

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